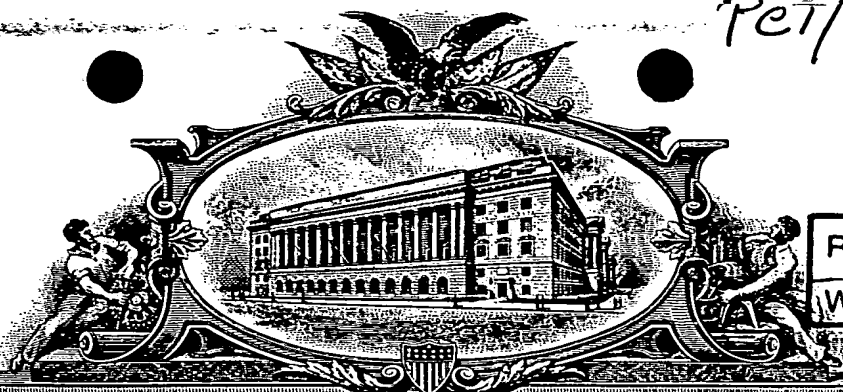


PCT/BE 96/00002



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# THE UNITED STATES OF AMERICA

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April 22, 1996

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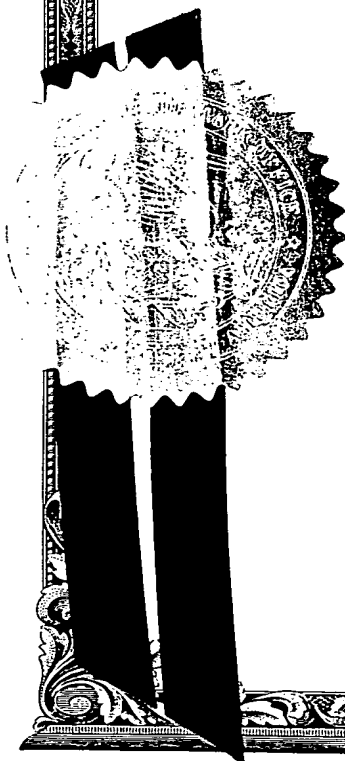
**APPLICATION NUMBER: 08/370,883**

**FILING DATE: January 10, 1995**

**PRIORITY DOCUMENT**

**By Authority of the  
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*K. R. Pridgen*  
**K. R. PRIDGEN**  
Certifying Officer



PATENT APPLICATION SERIAL NO. 8/370883

U.S. DEPARTMENT OF COMMERCE  
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FEE RECORD SHEET

100 MG 01/26/95 083 0884  
100 MG 01/26/95

1 101

730.00 CK 4040-003-0  
30.00 CK 4040-003-0

PTO-1556  
(5/87)

TITLE OF THE INVENTION

PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE

BACKGROUND OF THE INVENTION

5 Field of the Invention:

The present invention relates to a pharmaceutical dosage form of fenofibrate having enhanced bioavailability, as well as to an advantageous process for making the same.

Description of the Background:

10 Fenofibrate or p-(4-chlorobenzoyl)-phenoxy isobutyrate isopropyl ester is useful for the treatment of adult patients with very high elevations of serum triglyceride levels and/or cholesterol levels. The usual daily dosage is 300 mg which is administered in two or three doses.

15 Fenofibrate is absorbed as fenofibric acid which is responsible for the pharmacological activity. Fenofibric acid resulting from the hydrolysis of fenofibrate is extensively bound to plasma albumin. The plasma half-life is about 20 hours. Fenofibric acid is excreted  
20 predominantly in the urine, mainly as the glucuronide conjugate, but also as a reduced form of fenofibric acid and its glucuronides.

Fenofibrate, is presently available in a pharmaceutical dosage form consisting of hard gelatin  
25 capsules containing fenofibrate, lactose starch and magnesium stearate. After oral administration, during a meal, about 60% of the dose of this conventional form is

effectively absorbed and found in the blood as fenofibric acid, the main metabolite responsible for pharmacological activity. (Strolin & Al, Act Pharmacol. Toxicol. 1986; 59 (Suppl. 5); 167).

5       The first attempt to improve the bioavailability of fenofibrate was performed by Ben-Armor and Al, by solubilizing the fenofibrate in dimethyl isosorbide, a nonaqueous solvent with a miscible wetting agent (Labrafil M 1944CS) with HLB of between 3-4. In order to use the  
10       product in capsules, colloidal silicon oxide was added to increase the viscosity. The liquid so obtained was placed in hard gelatin capsules which, to be leak proof, were sealed. In vivo studies with this formulation indicate that there was no statistically significant difference in  
15       bioavailability between this liquid formulation and the conventional form when the product was given with food.

      European Patent Application 0330532 discloses a fenofibrate composition wherein the fenofibrate powder is co-micronized with a solid wetting agent. Sodium lauryl  
20       sulfate is described as the solid wetting agent of choice. The co-micronized powder so obtained is mixed with capsule filling excipient such as lactose, starch, polyvinyl pyrrolidone and magnesium stearate. A formulation of this composition is actually available on the French market  
25       under the trade name Lypantyl 200 M®. A study comparing this formulation (Lypantyl 200 M®) to the conventional form

was undertaken and a statistically significant increase in bioavailability was indicated for the former. In particular, it was found that 67 mg of the new form gives the same amount absorbed as does 100 mg of the conventional form. (J.L. Suichard & Al Cun Therapeutic Research Vol. 54, NS, Nov. 1993).

Unfortunately, co-micronization of the active drug fenofibrate with the wetting agent sodium lauryl sulfate, although necessary, is a time consuming and costly operation. Further, an inherent drawback of micronization is that the material obtained must comply with very stringent particle size specifications.

Moreover, the filling of hard gelatin capsules with a micronized powder is a difficult operation, particularly if weight variation homogeneity is considered.

Hence, a need exists for a fenofibrate formulation that avoids the use of co-micronization, while providing a bioavailability comparable to that afforded by the conventional fenofibrate formulation which uses co-micronization.

#### SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide a fenofibrate formulation not requiring use of co-micronization which, nevertheless, exhibits a

bioavailability comparable to formulations of fenofibrate which do.

It is also an object of the present invention to provide a solid, oral dosage form of a fenofibrate formulation that can be prepared by melting the excipients in which the fenofibrate is soluble and, therefore, does not require any particle size specification.

The above objects and others are provided by a pharmaceutical composition for treating hyperlipidemia in and/or hypercholeslerolemia a mammal, which contains an effective amount of each of fenofibrate and an excipient containing one or more polyglycolized glycerides.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a pharmaceutical formulation for treating hyperlipidemia and/or hypercholesterolemia in a mammal, which contains an effective amount of each of a fenofibrate composition and an excipient which contains one or more polyglycolized glycerides, the polyglycolized glycerides preferably having an HLB value of at least about 10.

The prevent invention is also particularly advantageous for the production of oral solid dosage forms which can be prepared by melting the excipients in which the fenofibrate is soluble, whereby particle size specifications are not required.

The present invention also relates to the addition of a suspension stabilizer to the molten solution of fenofibrate-polyglycolized glycerides. The suspension stabilizer avoids the formation of fenofibrate crystals during the cooling of the filled hard gelatin capsules. Suitable suspension stabilizers which may be used are, for example, cellulose derivatives, such as hydroxypropylcellulose, hydroxypropylmethyl cellulose, methyl cellulose, and hydroxyethylcellulose, povidone, poloxamers,  $\alpha$ ,  $\Omega$ -hydroxy-poly(oxyethylene) poly(oxypropylene)-poly(oxyethylene) bloc polymers. Other suspension stabilizers equivalent to these stabilizers may, of course, also be used.

The present invention is also particularly advantageous for the production of a pharmaceutical composition in that the hot, homogeneous fenofibrate solution is filled in hard gelatin capsules. This filling process permits the obtention of very precise fenofibrate amounts in each capsule.

The present invention is particularly advantageous as well for the production of the present pharmaceutical composition in that the process for manufacturing the composition requires very few steps such as melting, mixing and filling. This renders the present manufacturing process extremely cost effective when compared to one using co-micronization of powders.

Polyglycolized glycerides which may be used in the present invention are generally mixtures of known monoesters, diesters and triesters of glycerols and known monoesters and diesters of polyethylene glycols with a mean  
5 relative molecular mass between about 200 and 6000. They may be obtained by partial transesterification of triglycerides with polyethylene glycol or by esterification of glycerol and polyethylene glycol with fatty acids using known reactions. Preferably, the fatty acid component  
10 contains 8-22 carbon atoms, particularly 10-18 carbon atoms. Examples of natural vegetable oils which may be used include palm kernel oil and palm oil. However, these are only examples. The polyol suitably has a molecular weight in the range of about 200-6000 and preferably  
15 contains polyethylene glycol, although other polyols may be employed, such as polyglycerols or sorbitol. They are available on the market under the trade name Gelucire®.

As noted above, the HLB of the polyglycolized glycerides is preferably at least about 10, and more  
20 preferably between about 12 and 15. The melting point of the polyglycolized glycerides may be between about 18°C and 60°C. However, it is especially desirable to use polyglycolized glycerides having a melting point above 30°C, and preferably above 35°C, since there is no need for  
25 sealing the capsule, to assure the leak proofness thereof, when such excipients are used.



Further, two or more polyglycolized glycerides may be mixed in order to adjust both the HLB value and the melting point to a desired value. The HLB value and melting point of the composition may further be adjusted with the addition of components such as polyethylene glycols, polyoxyethylene glycols fatty acid esters, and fatty acid alcohols. In view of the present specification, it is well within the skill of the artisan to mix the polyglycolized glycerides to obtain desired HLB values and melting points.

It has also been discovered that the present composition affords an increased bioavailability of the fenofibrate as compared to conventional formulations.

Although the present inventors do not wish to be bound by any particular theories, one plausible mechanism of operation for the present invention is that upon cooling, the melted mixture of hot fenofibrate-polyglycolized glycerides maintains the fenofibrate in liquid form. When absorbed in the gastrointestinal tract of a patient, the gastrointestinal fluids are able to dissolve the fenofibrate due to the HLB value of the excipient mixture, whereby fenofibrate is readily absorbed.

Generally, the composition of the present invention contains from about 5% to 95% by weight of fenofibrate and from about 95% to 5% by weight of excipient including one or more polyglycolized glycerides. It is preferred, however, if the present composition contains from about 20%

to 80% by weight of fenofibrate and from about 80% to 20%  
by weight of excipient. It is even more preferred,  
however, if the present composition contains from about 30%  
to 70% by weight of fenofibrate and from about 70% to 30%  
5 by weight of excipient.

In a particularly preferred composition, generally  
about 45% to 55% by weight of fenofibrate is used and about  
55% to 45% by weight of excipient containing the one or  
more polyglycolized glycerides is used.

10 Generally, the method of the present invention entails  
adding one or more excipients, including the one or more  
polyglycolized glycerides to containing means and then  
heating the excipients until all components are melted.  
Then, fenofibrate is added slowly with continuous stirring  
15 until all fenofibrate added is dissolved. Stirring is then  
continued for about 10 minutes to about 1 hour, and  
preferably for about 15 minutes to about 30 minutes. Then,  
containing means for the pharmaceutical composition, such  
as hard gelatin capsules, are filled with the composition  
20 using a liquid filling capsule machine having dosing pumps  
which are heated to the same temperature as the temperature  
of the molten pharmaceutical composition. Generally, this  
temperature is about 55°C to about 95°C, more typically in  
the range of about 80°C to 90°C. Upon cooling to ambient  
25 temperature, the capsules are packed in bottles. When

capsules of size 3 are used, each capsule so prepared contains 67 mg of fenofibrate.

It is advantageous, however, to use the following protocol. To about 3 parts by weight polyglycolized  
5 glyceride excipient having a melting point of 44°C and an HLB value of 14 molten at 80°C, is added about 2 parts by weight of fenofibrate and about 1 part by weight of hydroxypropyl cellulose. After maintaining the solution  
10 under agitation for about 20 additional minutes, hard gelatin capsules are filled therewith.

The present invention will now be further described by reference to certain examples which are provided solely for purposes of illustration and are not intended to be  
limitative.

15

EXAMPLE 1

Fenofibrate	6.7 kg
Gelucire® 44/14	5.0 kg
Polyoxamer 407	<u>5.0 kg</u>
	16.7 kg

20

In a stainless steel container, were introduced 5 kg of Gelucire® 44/14 and 5 kg of Poloxamer 407, which were then heated at 85°C until all components are molten. 6.7  
kg of fenofibrate was added slowly while continuously stirring the mixture. When all of the fenofibrate was  
25 dissolved agitation was maintained for about twenty

minutes. Using a liquid filing capsule machine with dosing pumps heated at 85°C, capsules of size 3 was filled with 167 mg of solution. Upon cooling at room temperature the capsules were packaged in bottles. Each capsule so  
5 prepared contained 67 mg of fenofibrate.

#### PHARMACOKINETICAL STUDY

The composition of Example 1 was compared to conventional form in a pharmacokinetical study with 15 healthy subjects. Each subject received 3 capsules of  
10 composition of Example 1 (201 mg of fenofibrate) or 3 capsules of Ly pantyl 100® (300 mg of the conventional form). The sessions were separated by a wash out period of 7 days. The medications were taken after a high-fat  
15 different times up to 72 hours after administration. The plasma concentration of fenofibric acid was determined in all available samples using a conventional HPLC method.

Plasma Fenofibric Acid Concentration (mg/l vs. time (h) After Administration at 3 Capsules of Example 1 (Total amount of Fenofibrate administered: 201 mg)																
Post-dose time (h)	1	2	3	4	5	6	8	9	10	11	12	13	14	15	16	SD
0	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	0
1	BLOQ	BLOQ	0.42	BLOQ	0.52	0.81	0.29	BLOQ	0.32	BLOQ	BLOQ	BLOQ	BLOQ	0.81	BLOQ	0.21
2	0.36	0.34	3.87	4.31	5.10	6.00	4.66	6.46	2.56	BLOQ	BLOQ	1.09	3.84	3.01	0.75	2.89
3	3.31	1.06	7.52	8.12	12.80	7.68	7.50	7.27	6.55	2.51	3.83	3.22	12.68	6.73	5.62	6.43
4	4.06	2.70	6.02	10.87	13.56	8.27	9.42	8.93	8.16	4.46	5.35	5.23	13.93	7.17	9.61	7.85
5	4.06	5.49	6.61	10.84	12.65	6.99	9.64	11.70	9.65	6.49	7.42	5.46	14.41	8.53	11.08	8.73
6	4.32	7.17	6.42	10.68	12.34	6.32	12.19	16.75	11.64	9.75	12.16	5.76	15.68	9.95	13.70	10.32
7	3.82	7.60	4.28	8.50	11.75	5.68	8.93	8.45	11.43	8.89	11.41	3.74	7.60	9.06	10.72	8.12
9	4.74	6.83	3.71	6.28	9.61	4.27	8.12	6.19	9.97	6.80	8.79	3.57	7.41	6.42	8.70	6.76
12	5.61	8.07	2.36	5.66	8.08	3.49	7.05	4.70	7.78	5.00	7.00	6.25	3.75	4.83	6.49	5.74
24	2.57	3.56	0.85	2.48	4.78	1.39	2.51	1.83	3.40	2.19	2.12	2.30	3.67	2.29	2.64	2.59
36	1.24	1.53	0.61	1.64	3.01	0.63	1.73	1.16	2.38	1.42	1.64	1.24	1.74	1.26	1.26	1.50
48	0.80	0.76	0.27	0.98	2.13	0.29	1.05	0.95	1.54	1.06	1.10	0.63	1.33	0.73	0.88	0.97
60	0.55	0.70	BLOQ	0.64	1.43	0.28	0.73	0.43	0.88	0.73	0.92	0.28	0.78	0.48	0.70	0.64
72	0.40	0.52	BLOQ	3.50	1.21	BLOQ	BLOQ	0.38	0.68	0.51	0.53	BLOQ	0.62	BLOQ	0.39	0.34

Plasma Fenofibric Acid Concentration (mg/l vs. time (h) After Administration at 3 Capsules of the Conventional Form (Total amount of Fenofibrate administered 300 mg)																
Post-dose time (h)	1	2	3	4	5	6	8	9	10	11	12	14	15	16		
0	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ		
1	BLOQ	BLOQ	BLOQ	0.25	BLOQ	BLOQ	1.90	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ		
2	BLOQ	BLOQ	0.25	4.67	0.34	1.52	5.83	BLOQ	BLOQ	0.42	0.63	BLOQ	BLOQ	1.28		
3	1.76	0.99	2.16	7.39	4.51	3.72	5.89	2.45	1.53	1.71	1.55	1.03	0.47	3.79		
4	3.24	4.62	5.57	9.13	8.81	5.00	5.76	5.12	6.54	4.37	3.58	3.47	4.75	5.08		
5	4.53	10.24	12.20	12.16	10.43	4.77	6.57	11.97	12.91	4.93	6.94	4.22	6.40	11.35		
6	8.77	17.36	12.93	12.08	13.18	5.66	6.62	14.17	18.00	9.03	11.45	4.30	11.12	10.65		
7	4.75	11.92	12.12	10.71	11.36	4.84	5.90	12.31	14.42	8.08	10.59	4.17	13.21	10.11		
9	3.64	8.21	9.29	8.39	9.62	6.34	5.80	7.33	10.86	6.37	8.25	6.34	10.22	7.21		
12	4.24	7.03	6.20	6.90	7.96	8.66	5.30	6.67	7.50	5.11	7.09	12.05	9.16	5.74		
24	2.36	3.43	1.88	3.12	4.76	2.53	2.19	2.61	2.85	2.66	2.85	6.53	4.92	2.29		
36	1.17	2.03	0.92	1.56	3.27	0.95	1.47	1.14	1.73	1.48	1.38	3.31	2.31	1.33		
48	0.70	1.17	0.61	1.02	2.06	0.49	0.71	0.94	0.90	1.07	0.92	1.72	1.39	0.81		
60	0.49	0.50	0.43	0.66	1.77	0.31	0.74	0.81	0.58	0.69	0.55	0.81	1.13	0.54		
72	BLOQ	BLOQ	0.30	0.49	1.48	BLOQ	0.49	0.54	0.34	0.52	0.40	BLOQ	0.83	0.35		

The bioavailability, as measured by the extent of absorption (AUC) indicates, that 3 capsules of Example 1 of the present invention (201 mg of fenofibrate AUC = 195) are bioequivalent to 3 capsules of the conventional form (300 mg of fenofibrate AUC = 221).

That is, the bioavailability of fenofibrate from the composition of Example 1 of the present invention is 1.5 times higher than the bioavailability of fenofibrate of the conventional form.

EXAMPLE 2

Fenofibrate	5 kg
Gelucire® 44/14	7.5 kg
Carbowax 20,000	1.5 kg
Hydroxypropylcellulose	<u>2.5 kg</u>
	16.5 kg

To a heated kettle, 7.5 kg of Gelucire® 44/14 and 1.5 kg of carbowax 20,000 were added and then heated at 85°C until all components are molten. 5 kg of fenofibrate was added slowly while continuously stirring. When all the fenofibrate was dissolved, 2.5 kg of hydroxypropylcellulose was added and agitation was maintained for about twenty minutes. Using a liquid filling capsule machine with dosing pumps heated at 85°C, capsules of size 0 were filled with 660 mg of solution. Upon cooling at room temperature the capsules were packaged in bottles. Each capsule so

prepared contained 200 mg of fenofibrate. 12,701 capsules were produced and individually weighed. Results of the capsule weighing is shown in Table 3.

TABLE 3 Capsules Weight Variations From 12,701 Capsules		
5	Theoretical Weight	764.5 mg
	Mean weight of acceptable capsules (95-105%)	763.9 mg
	Standard Deviation of Accepted Capsules	6.9 mg
10	Relative Standard Deviation of Accepted Capsules	0.9%
	Percent of Rejected Capsules (below 95% of Theoretical Amount)	0.307%
15	Percent of Rejected Capsules (above 105% of Theoretical Amount)	0.039%

It may readily be appreciated from Table 3 that the filling process of the present invention is extremely accurate.

#### PHARMACOKINETICAL STUDY

The composition of Example 2 of the present invention was compared during a Pharmacokinetical study to the co-micronized formulation available on the French market (Lypanthyl 200 M®).

The study was conducted as a single dose, randomized, four-way cross over study in 8 healthy subjects. The



subjects were randomly assigned to one of four administration sequences. On each of the four sessions, separated by wash-out periods of 7 days, the subjects received either 200 mg of fenofibrate under the form  
5 Lypanthyl 200 M® or 200 mg of fenofibrate under the form of Example 2 with and without a high-fat breakfast. Blood samples were taken before and at different times up to 72 hours after administration. The plasma concentrations of fenofibric acid was determined in the samples using on HPLC  
10 Method..

The pharmacokinetics parameters obtained are shown in Table 4.

15 TABLE 4 Pharmacokinetical Parameters After Administration of Lypanthyl 200 M® and Composition of Example 2 Taken With and Without a High Fat Breakfast (Dose 200 mg of Fenofibrate)

	Without Food		With Food	
	Example 2	Lypanthyl 200M®	Example 2	Lypanthyl 200M®
AUC <sub>0-72</sub>	107.0	101.0	181.0	184.7
C <sub>max</sub>	5.1	5.9	11.1	10.9
t <sub>max</sub>	5.9	5.2	5.2	5.7

20 The present composition may thus be advantageously used to treat hyperlipidemia and/or hypercholesterolemia in humans. Generally, the effective daily amount of fenofibrate from humans ranges from about 100 mg to 600 mg per day, and preferably from about 100 to 300 mg per day,  
25 with the precise amount being determined by the attending

physician, considering such parameters as condition severity and body weight, for example.

Having fully described the present invention, it will be apparent to one of ordinary skill in the art that many  
5 changes and modification may be made to the above-described embodiments without departing from the spirit and scope of the present invention.

WHAT IS CLAIMED AS NEW AND DESIRED TO BE SECURED BY LETTERS  
PATENT OF THE UNITED STATES IS:

1. A pharmaceutical composition for treating  
hyperlipidemia or hypercholesterolemia or both in a mammal,  
5 which comprises an effective amount of each of fenofibrate  
and an excipient comprising one or more polyglycolized  
glycerides.

2. The composition of Claim 1, wherein said  
fenofibrate is present in an amount of 5% to 95% by weight  
10 based on the total weight of the composition.

3. The composition of Claim 1, wherein the  
polyglycolized glycerides have a HLB value of at least 10.

4. The composition of Claim 3, wherein the  
polyglycolized glycerides have a HLB value of from 12 to  
15  
15 15.

5. The composition of Claim 1, which further  
comprises polyalkylene glycols to adjust the HLB value or  
melting point or both to the desired value.

6. The composition of Claim 1, wherein a suspension  
20 stabilizer is added.

7. The composition of Claim 6, wherein said  
suspension stabilizer is selected from the group and  
consisting of cellulose, povidone, poloxamers,  $\alpha$ ,  $\Omega$ -  
hydroxy-poly(oxyethylene) poly(oxypropylene)-  
25 poly(oxyethylene)bloc polymers.

8. The composition of Claim 1, in which said fenofibrate and said excipient are in unit dosage form and are contained in a hard gelatin capsule.

9. The composition of Claim 8, wherein said hard  
5 gelatin capsule contains from about 67 mg to about 200 mg of fenofibrate.

10. A method of making a solid oral dosage form of a pharmaceutical composition, comprising an effective amount of each of fenofibrate and an excipient comprising one or  
10 more polyglycolyzed glycerides, which method comprises adding said molten fenofibrate and said excipient to hard gelatin capsules, and allowing said said molten fenofibrate and said excipient to cool therein.

11. A method of treating hyperlipidemia or  
15 hypercholesterolemia or both in a mammal in need thereof, which comprises administering to said mammal an effective amount of a pharmaceutical composition, comprising fenofibrate and an excipient containing one or more polyglycolyzed glycerides.

20 12. The method of Claim 11, wherein said mammal is human, and said effective amount of fenofibrate in said composition is from about 100 mg to 600 mg per day.

13. The method of Claim 12, wherein said effective  
25 amount of fenofibrate in said composition is from about 100 mg to 300 mg per day.

14. The method of Claim 11, wherein said composition is administered orally.

15. The method of Claim 10, which is with the proviso that the fenofibrate used is not co-micronized.

ABSTRACT OF THE DISCLOSURE

A pharmaceutical composition is provided for treating hyperlipidemia or hypercholesterolemia or both in a mammal, which contains an effective amount of each of fenofibrate  
5 and an excipient containing one or more polyglycolized glycerides.

# Declaration, Power Of Attorney and Petition

Page 1 of 3

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name.

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

PHARMACEUTICAL COMPOSITION CONTAINING FENOELIBRATE

the specification of which

☐ is attached hereto.

☒ was filed on January 10, 1995 as

Application Serial No. 08/370,883

and amended on \_\_\_\_\_

☐ was filed as PCT international application

Number \_\_\_\_\_

on \_\_\_\_\_

and was amended under PCT Article 19

on \_\_\_\_\_ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under Section 119 of Title 35 United States Code, of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Application No.	Country	Day/Month/Year	Priority Claimed
_____	_____	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No

We (I) hereby claim the benefit under Section 120 of Title 35 United States Code, of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Section 112 of Title 35 United States Code, We (I) acknowledge the duty to disclose material information as defined in Section 1.56(a) of Title 37 Code of Federal Regulations, which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (pending, patented, abandoned)
_____	_____	_____
_____	_____	_____
_____	_____	_____

And we (I) hereby appoint: Norman F. Oblon, Registration Number 24,618; Marvin J. Spivak, Registration Number 24,913; C. Irvin McClelland, Registration Number 21,124; Gregory J. Maier, Registration Number, 25,599; Arthur I. Neustadt, Registration Number 24,854; Robert C. Miller, Registration Number 25,357; Richard D. Kelly, Registration Number 27,757; James D. Hamilton, Registration Number, 28,421; Eckhard H. Kuesters, Registration Number 28,870; Robert T. Pous, Registration Number 29,099; Charles L. Gholz, Registration Number 26,395; Vincent J. Sunderdick, Registration Number 29,004; William E. Beaumont, Registration Number 30,996; Steven B. Kelher, Registration Number 30,073; Stuart D. Dwork, Registration Number 31,103; Robert F. Gnuse, Registration Number 27,295; Jean-Paul Lavalleye, Registration Number 31,451; William B. Walker, Registration Number 22,492; Timothy R. Schwartz, Registration Number 32,171; Stephen G. Baxter, Registration Number 32,884; Gilberto M. Villacorta, Registration Number 34,038; and John H.O. Clarke, Registration Number 17,373; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Arthur Deboeck  
NAME OF FIRST SOLE INVENTOR

Arthur Deboeck  
Signature of Inventor

March 14, 95  
Date

Residence: c/o Galephar P.R. Inc.  
Ave Iturregui Calle B  
P.O. Box 3468  
Carolina, Puerto Rico 00984-3468  
Citizen of: Belgium  
Post Office Address: \_\_\_\_\_  
Same as Above



Paul Maes  
NAME OF SECOND JOINT INVENTOR

[Signature]  
Signature of Inventor

12/1/95  
Date

Phillipe R. Baudier  
NAME OF THIRD JOINT INVENTOR

[Signature]  
Signature of Inventor

1/13/95  
Date

16/3/95  
NAME OF FOURTH JOINT INVENTOR

\_\_\_\_\_  
Signature of Inventor

\_\_\_\_\_  
Date

\_\_\_\_\_  
NAME OF FIFTH JOINT INVENTOR

\_\_\_\_\_  
Signature of Inventor

\_\_\_\_\_  
Date

Residence: c/o Galephar P.R. Inc.  
Ave Iturregui Calle B  
P.O. Box 3468  
Carolina, Puerto Rico 00984-3468

Citizen of: Belgium

Post Office Address: \_\_\_\_\_  
Same as Above

Residence: c/o Galephar P.R. Inc.  
Ave Iturregui Calle B  
P.O. Box 3468  
Carolina, Puerto Rico 00984-3468

Citizen of: France

Post Office Address: \_\_\_\_\_  
Same as Above

Residence: \_\_\_\_\_

Citizen of: \_\_\_\_\_

Post Office Address: \_\_\_\_\_

Residence: \_\_\_\_\_

Citizen of: \_\_\_\_\_

Post Office Address: \_\_\_\_\_